circumstance the maternal mortality rate is 25% or higher, it can also occur after induced abortions and miscarriages and spontaneously during the second and third trimesters. AFE can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, AFE is responsible for 13 to 30% of maternal deaths and is the fifth leading cause of direct maternal death.[59]

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. Half of the cases of mortality occur during the first 2 hours when vasospasm, release of vasoactive substances, and mechanical plugging of vessels, particularly in the maternal pulmonary vascular tree, trigger abrupt cardiopulmonary collapse.[59] In survivors, disseminated intravascular coagulation, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 10% of patients. Bleeding diathesis may be the initial sign in some women.

Diagnostic Strategies

When AFE is suggested, a complete blood cell count, coagulation studies, arterial blood gases, and chest radiograph should be obtained. Urinary output should be monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.[59]

Differential Considerations

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizure occurs in patients with eclampsia, but in that condition hypertension, rather than cardiovascular collapse, should be observed. Coagulopathy may be seen in patients with preeclampsia (HELLP syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Management

Amniotic fluid embolus is uncommon, so treatment is mainly anecdotal and based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. A few reports have indicated that plasma exchange may be helpful to remove triggering cytokines.[60] Adequate management usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, but the maternal immune system is only triggered by significant loads of fetal cells, which can occur during the third trimester and at delivery. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. To prevent this, anti-D immunoglobulin (RhoGAM) is routinely administered to Rh-negative mothers (if the father is Rh-positive or his status is unknown) at approximately the 28th week of gestation to protect the mother from spontaneous sensitization, which occurs during the third trimester. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immunoglobulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies only carry the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immunoglobulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.[10]

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immunoglobulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy; RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks.[46] In instances of significant blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare large fetal transfusions that may require specific fetal blood therapy or administration of additional immunoglobulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.[10]

■ MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Perspective

Clinicians must be aware of a variety of illnesses, both related and unrelated to pregnancy, that may have altered symptomatology, risk, and treatment in the pregnant patient (Tables 176-2 and 176-3).

Abdominal Pain

Gynecologic Problems

Several gynecologic diseases must be considered in evaluating the pregnant patient who has abdominal pain. These include threatened miscarriage and ectopic pregnancy, which were discussed previously in this chapter. A patient with either complication of pregnancy can complain of nonspecific abdominal pain, either in the midline or laterally, and may show intermittent or constant symptoms. A careful history can be helpful in differentiating gradual progression of inflammatory or infectious diseases (e.g., ovarian cyst expansion or, rarely, PID) from sudden peritonitis caused by spillage of blood or cyst fluid into the peritoneal cavity or from the colicky pain of renal stones or the ischemic pain of ovarian torsion. In addition, examination of the abdomen, back, and pelvis helps localize the pain to areas and specific organs, thus narrowing

Table 176-2 Differential Diagnosis of Abdominal Pain in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Gynecologic		
Miscarriage	<20 wk, 80% <12 wk	Ultrasonography to confirm location
Septic abortion	<20 wk	Fever, uterine tenderness
Ectopic pregnancy	<14 wk	Must always consider in first trimester until intrauterine pregnancy confirmed
Corpus luteum cyst	<12 wk	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 wk	Ischemic pain
Pelvic inflammatory disease	<12 wk	Very rare
Chorioamnionitis	>16 wk	Tender uterus, fever; amniocentesis reveals white blood cells
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 wk	Hypertension, proteinuria, edema, right upper quadrant pain
Nongynecologic		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

Table 176-3 Differential Diagnosis of Common Symptoms in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Vaginal Bleeding		
Miscarriage	<20 wk	Usually no fetal heart activity at 8 weeks; decreasing hCG
Ectopic pregnancy	<14 wk	Evaluate with ultrasonography
Molar pregnancy	12–24 wk	No fetal heart tones, characteristic sonogram
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis/cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 wk	Ultrasonography to localize placenta
Abruptio placentae	>16 wk	Ultrasonography to exclude previa; fetal distress, tenderness
Seizure		
Eclampsia	>24 wk	Blood pressure >140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 wk	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
Dyspnea		
Pulmonary embolus	Especially 6 wk prepartum and postpartum	Usual diagnostic studies
Dyspnea of pregnancy	>24 wk	Exclude other causes
Pulmonary infection	Throughout	Examination; roentgenography
Amniotic fluid embolus	>12 wk	Uterine manipulation, bleeding diathesis, hypotension
Jaundice		
Cholestasis of pregnancy	>24 wk	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function tests
Acute fatty liver	>24 wk	Rapid liver failure; coma, seizures, hypoglycemia
Bleeding Diathesis		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 wk	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 wk	Uterine tenderness; vaginal bleeding; fetal distress

DIC, disseminated intravascular coagulation; hCG, human chorionic gonadotropin; HELLP, hemolysis, elevated liver enzymes, low platelets; PIH, pregnancy-induced hypertension.

the differential diagnosis and guiding the selection of ancillary studies.

Appendicitis

Perspective. Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which results in significant fetal mortality and maternal morbidity.[61,62] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes less classic during the second half of pregnancy.

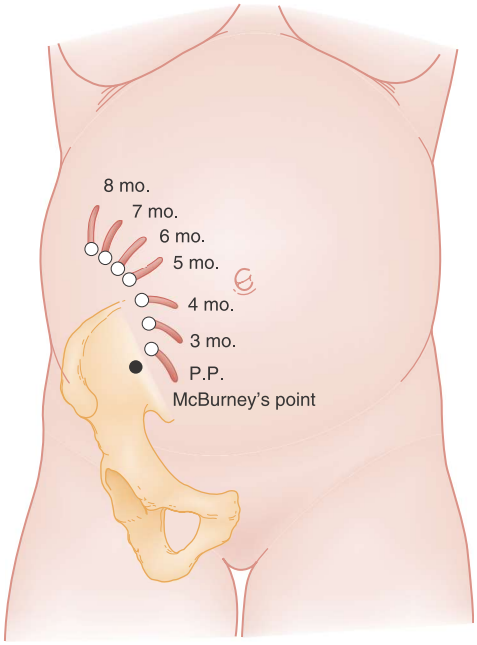

Figure 176-8. Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretical location of the appendix. P.P., postpartum. (From Gabbe SG, et al [eds]: Obstetrics: Normal and Problem Pregnancies. New York, Churchill Livingstone, 2007; as modified from Baer JL, Reis RA, Arens RA: Appendicitis in pregnancy. JAMA 98:1359, 1932.)

Principles of Disease. Traditionally, the appendix was thought to displace counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 176-8). However, a study has questioned this finding; it found that in only 23% of pregnant patients did the location change from the right lower quadrant, even in the third trimester.[62] Displacement of the abdominal wall away from the abdominal viscera can result in difficulty palpating organs and loss of signs of parietal peritoneal irritation. The physiologic increase in white blood cell count and erythrocyte sedimentation rate in pregnancy must also be considered when evaluating the patient with possible appendicitis because these may confuse the overall clinical picture.

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are likewise most common during the first trimester. Lack of fever, leukocytosis, or tachycardia has been reported.[63,64] The cause of these differences in clinical findings in pregnant patients with appendicitis may be a blunted inflammatory response from elevated maternal levels of pregnancy-related steroids. Pyuria without bacteruria is seen in up to 58% of patients.[65]

Because of confounding factors, the misdiagnosis rate for appendicitis is 30 to 35% overall in pregnancy, with a 40 to 50% rate of removal of normal appendix during the third trimester.[63,65,66] In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required even in the absence of classic signs. In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed and the perforation rate may approach 25%.

Differential Considerations. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion must be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix takes up a position very near the kidney, resulting in a high incidence of pyuria and flank pain (see Fig. 176-8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Strategies. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. Pyuria in a catheterized urine specimen suggests pyelonephritis, but it is also seen in 20% of patients with appendicitis.[63] Bacteruria is uncommon. Ultrasonography, using graded-compression techniques, may reveal a noncompressible tubular structure in the right lower quadrant consistent with appendicitis. Studies regarding the diagnostic utility of ultrasonography in the diagnosis of appendicitis are limited but suggest that it has a high positive predictive value but a low negative predictive value.[65,67] Given the low radiation risk to the fetus, the noninvasive nature of the test, and its utility in evaluating other complications, some authors have recommended that ultrasonography should be the initial test of choice when appendicitis is suspected, especially in the first and second trimesters.[64,65] Castro and colleagues[68] reported the utility of helical CT in diagnosis, with fetal radiation exposures of only 300 mrad, using rectal contrast and a limited study. Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient suspected of having appendicitis. Early exploration is to be encouraged even more in pregnant than in nonpregnant patients because of the variability of clinical signs and the increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be admitted to the hospital after appropriate consultation with surgeons and obstetricians. Ultrasonography or CT scan should be considered as diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with intravenous fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases a period of inpatient observation may allow clarification of signs and symptoms.

Gallbladder Disease

Perspective. Cholelithiasis is present in approximately 5% of pregnant women and is the second most common nonobstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than half of patients with gallstones developing symptoms.[69,70]

Principles of Disease. Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.[71]

Clinical Features. The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant

women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the increased white blood cell count seen normally in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of self-limited pain episodes associated with food intake is useful in suggesting the diagnosis.

Diagnostic Strategies. Ultrasonography is a reliable means of recognizing stones within the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Differential Considerations. Pyelonephritis should always be considered in the patient with right upper quadrant pain with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur in late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should always be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Management. The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given IV fluid hydration, adequate pain control, and broad-spectrum antibiotics. These patients must be admitted for inpatient management. Some patients can be managed medically for prolonged or complicated cholecystitis. Patients with obstructive jaundice, gallstone pancreatitis, or sepsis or patients who fail conservative management should have surgery. Discharge should be considered only in patients with uncomplicated and sonographically proven cholelithiasis who do not meet admission criteria after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse.[72] Early follow-up should be arranged and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain. In one study, one third of pregnant women with biliary colic failed conservative treatment but were treated safely, often using newer laparoscopic techniques.[73]

Liver Disorders

Perspective. Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Clinicians should recognize the various symptoms of liver disease during pregnancy as well as the hepatic diseases unique to pregnant women. Liver metabolism increases during pregnancy, but hepatic blood flow is unchanged and little change occurs in liver function. Bilirubin, transaminases, lactate dehydrogenase, and prothrombin times are unchanged from the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphate levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.[74-76]

Hepatitis. Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice in pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E, however, has been reported to have a more aggressive course in pregnancy.[76] Maintaining adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Prophylaxis should be administered to the newborn.

Acute Fatty Liver of Pregnancy. Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

Principles of Disease. The cause of acute fatty liver of pregnancy is unknown, although studies suggest that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation.[76-79] Microscopically, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related.[76] The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.[76,77]

Clinical Features. Nausea and vomiting or liver dysfunction during the third trimester should trigger consideration of a diagnosis of acute fatty liver. In addition, nonspecific flulike symptoms, such as anorexia, fatigue, and headache, occur initially.[80] The right upper quadrant and/or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, disseminated intravascular coagulation, and hepatic encephalopathy. The diagnosis is often delayed secondary to the multiple differential considerations.[81]

Diagnostic Strategies. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin time and partial thromboplastin time are elevated, and fibrin split products are present. Hypoglycemia may occur. Serum transaminase levels are elevated, although rarely above 1000 U/L (a distinguishing feature from hepatitis), and should be measured in all patients who have systemic gastrointestinal symptoms during the third trimester. In contrast to Reye's syndrome, the serum ammonia level is only mildly elevated. Hyperuricemia is usually present. Bilirubin is elevated late in the course of the disease. The CT scan is usually normal, as is the sonogram. Liver biopsy is used to make the definitive diagnosis.[82]

Differential Considerations. Liver tenderness and coagulopathy most often suggest preeclampsia during the third trimester.[82] Jaundice and increases in aminotransferase level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy is unlikely in cases of preeclampsia. The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screen for acetaminophen or other toxins if appropriate. Cholecystitis may be distinguished by ultrasound, but it may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure.

Management. The patient with acute fatty liver of pregnancy requires immediate stabilization if experiencing seizure or coma. Hypoglycemia may occur, which should be rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease

has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. The route of delivery is dictated by the patient's clinical course and hemodynamic status. Fresh frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished. After delivery, infants of mothers with acute fatty liver of pregnancy are at risk for postpartum hypoglycemia and liver dysfunction and therefore should be monitored closely.[82]

Intrahepatic Cholestasis of Pregnancy. Intrahepatic cholestasis of pregnancy, also termed *idiopathic jaundice of pregnancy*, *icterus gravidarum*, or *pruritus gravidarum*, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. Histologically, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, with multiple gestations, and in the winter months.[76,80]

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. Only 20% of patients present with this combination, however, and 80% present with pruritis alone. The pruritis usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated 7- to 10-fold, and transaminase levels are in the normal range. Resolution occurs when the woman delivers. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.[76,80,83]

Differential Considerations and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, or complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some authors advocate aggressive fetal surveillance and delivery after fetal lung maturity to improve fetal outcome.[76] Symptomatic treatment with antihistamines, ursodeoxycholic acid, bile salts, guar gum, benzodiazepines, and other medications has been tried with variable success.[80,84]

Hyperemesis Gravidarum

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. *Hyperemesis gravidarum* is defined as nausea and vomiting that causes starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. It occurs in a small minority of pregnant patients. The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels, as well as with maternal cytokines.[85,86] Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum.[87-89] Initial management involves rehydration with intravenous fluids, antiemetics, and demonstration of ability to take oral hydration. Patients may require enteral nutrition. Most standard antiemetics are in Food and Drug Administration category C and are used successfully to treat hyperemesis gravidarum. A short course of oral prednisolone has been reported to be therapeutic for intractable hyperemesis.[90,91] Oral vitamin B_6 has also been reported to be helpful.[89] Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal levels after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function tests, which are expected to resolve with supportive treatment.[92]

Thromboembolic Disease in Pregnancy

Principles of Disease

Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.[16] Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the puerperium. Women who smoke, are overweight, are older than 35 years, have varicose veins, or have a prior superficial venous thrombosis or history of a hypercoagulable state, as well as women who deliver prematurely or have postpartum hemorrhage, are at higher risk.[93-96]

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep vein thrombosis in pregnancy. The clinical diagnosis of pulmonary embolus is likewise difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with pulmonary embolus, the symptoms are nonspecific and may be associated with such diverse diseases as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Strategies

An arterial blood gas analysis should be undertaken, although it may be difficult to interpret. Arterial blood gases in pregnancy normally show a respiratory alkalosis from progesterone-induced respiratory stimulation, and the alveolar-arterial (A-a) oxygen difference is normal (the pregnant normal A-a gradient can be as high as 20 mm Hg) in the majority of patients with pulmonary embolus.[97] A chest radiograph (shielding the pelvis and uterus) should be obtained to exclude other disease processes that may mimic a pulmonary embolus. The diaphragm is normally symmetrically elevated during late pregnancy.

Noninvasive impedance plethysmography is highly accurate for the exclusion of deep vein thrombosis but lacks sensitivity for the exclusion of nonobstructive thrombi. Due to its widespread availability, Doppler ultrasonography has superseded noninvasive impedance plethysmography as the first-line test for the diagnosis of deep venous thrombosis. Both tests, however, are useful in the diagnosis of deep vein thrombosis of the femoral or popliteal veins in pregnancy, and these studies provide the least risk to the patient. Abnormal flow study results can be found in the normal patient studied in the supine position during late pregnancy, so positive results should be confirmed with the patient positioned on her left side. An unequivocally abnormal flow study finding is sufficient reason to treat the pregnant patient in most cases. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy and requires imaging with magnetic resonance imaging or CT for diagnosis. If thromboembolic disease is suspected, serial indirect Doppler testing or CT may be required.[98] The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Technetium-labeled ventilation-perfusion scans expose the fetus to less than 50 mrad of radiation, making them safe in all trimesters. One study found that only 2% of pregnant women

had high-probability scans; no adverse events occurred during follow-up in 104 women who were not heparinized and had normal or nondiagnostic scans.[99] Helical CT scanning provides an alternative for the diagnosis of pulmonary embolus in pregnancy. The average fetal radiation dose in helical CT scans is less than that from ventilation-perfusion scans, making it a potentially attractive alternative, although studies of its accuracy in pregnancy have not been done.[100] A pulmonary angiogram may be required if the diagnosis of pulmonary embolus is unclear after less invasive studies have been performed.

Management

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects and high risk of abortions and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy. Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with intravenous heparin is followed by subcutaneous heparin twice daily, usually continued for 3 to 6 months postpartum in patients who have deep vein thrombosis or pulmonary embolus during pregnancy. Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable in pregnancy. Low-molecular-weight heparin is considered safe in pregnancy and offers several advantages over unfractionated heparin: decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia.[101-105] In patients with a history of deep vein thrombosis or pulmonary embolus, prophylaxis for subsequent gestations is usually recommended.[106-108]

Genitourinary Infections

Urinary Tract Infection

Principles of Disease. Although the risk of asymptomatic bacteruria (9%) does not increase in pregnancy, it appears that pregnancy predisposes the patient to develop symptomatic lower and upper tract genitourinary infections.[109,110] Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis all appear to contribute to increased risk of infection during pregnancy.

Identification of patients with asymptomatic bacteruria by prenatal screening in early pregnancy identifies approximately 95% of individuals at risk for subsequent bacteruria during the pregnancy. Because up to 30% of women who have asymptomatic bacteruria will develop pyelonephritis if untreated, treatment of bacteruria is cost-effective and important.[111,112]

Clinical Features and Diagnostic Strategies. The pregnant patient who comes to the emergency department with lower urinary tract symptoms (e.g., dysuria, frequency, and urgency) or upper tract symptoms (e.g., fever, malaise, or back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen (preferably catheterized). There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings, either because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor.[112] The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the woman who has pyelonephritis is ominous and can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Considerations. Vaginitis, herpes genitalis, chlamydial infection of the urethra, or ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical cultures and to identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of upper urinary tract infection. Back pain may also be a sign of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to making the correct diagnosis.

Management. Patients with asymptomatic bacteruria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against usual urinary pathogens and is safe in pregnancy.[112,113] The most common choices are a cephalosporin, a nitrofurantoin, or a sulfonamide (except during the third trimester). Single-dose therapy for these infections during pregnancy has been proposed but may not be appropriate in an emergency department population with questionable follow-up and a relatively high incidence of occult upper urinary tract infection.

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for intravenous antibiotic administration, although outpatient parenteral therapy can be effective and safe in selected patients.[112,114] In such cases, aggressive intravenous hydration, obstetric consultation, and urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, cephalosporin or a combination of a penicillin and an aminoglycoside (which must be carefully monitored because of variable clearance by infected kidneys) is the usual intravenous medication administered. Cultures must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeat culture and be followed closely after treatment.

Vaginitis

Bacterial Vaginosis. Bacterial vaginosis (formally known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15 to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. Therapy during the second trimester is recommended even when the patient is asymptomatic to prevent the sequelae of premature rupture of membranes. Management includes a 7-day course of metronidazole or a 7-day course of clindamycin. Intravaginal treatment is not recommended in pregnant patients.[113,115]

Candida albicans *Vaginitis.* The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. It is not increased in the pregnant patient

who has recently been on antibiotics,[116] and there is no association of *Candida* colonization with adverse pregnancy outcomes.[117] Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes.[118] Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85 to 100% cure rate.[113] Recurrent disease may require a vaginal culture to confirm diagnosis and to identify unusual candidal species (e.g., *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's partner may also be required.

Trichomoniasis. Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, or vaginal irritation. Diagnosis is made by direct visualization or protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.[113] The organism is rarely aggressive during pregnancy but is associated with adverse pregnancy outcomes if untreated.[119]

Sexually Transmitted Diseases in Pregnancy

Sexually transmitted diseases are treated in pregnant patients according to the latest Centers for Disease Control and Prevention guidelines. In general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in preventing preterm labor and the morbidity of prematurity.

Chlamydia trachomatis *Infection.* *Chlamydia trachomatis* infection is the most common sexually transmitted disease, both in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection.[113] Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells. Routine chlamydia screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections.[120] Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects.[121] Treatment with a 7-day course of erythromycin base or amoxicillin is an acceptable alternative. Tetracyclines are contraindicated in pregnancy.[113]

Herpes Simplex Infection. Herpes simplex virus infections pose a significant risk in pregnancy to both the mother and the newborn. Women who have genital herpes during the third trimester have a 30 to 50% increased risk of transmission compared with women with herpes simplex virus infection in the first trimester (1%). The virus can be transmitted prenatally via transplacental infection or ascending vaginal infection and via vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the central nervous system, causing significant morbidity and mortality. In the emergency department, culturing of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir and valacyclovir use in pregnancy is not well-known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex virus occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex virus.[113,122-124] Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Neisseria gonorrhoeae *Infection.* Gonococcal infection of the cervix occurs during pregnancy in 1% of women. Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix. Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy, and treatment includes cephalosporins or spectinomycin.[113] Treatment for possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.[113,119]

Upper Genital Tract Infection

Pelvic Inflammatory Disease. Pelvic inflammatory disease is very rare in pregnancy and does not occur after the first trimester. Differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for chlamydia and gonorrhea should be obtained. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospital admission and intravenous antibiotics.[113]

Chorioamnionitis. Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. The diagnosis is confirmed by amniocentesis. Patients should have blood cultures drawn. Vaginal and cervical cultures for group B strep, *E. coli*, chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained, and hospital admission for intravenous antibiotics is required. Patients are usually treated with intravenous ampicillin and gentamicin. Vancomycin, clindamycin, or erythromycin may be substituted in the penicillin allergic patient.[125,126]

Acknowledgment

We thank Dr. Jean Abbott for her work on prior editions of this chapter.